IN THE SPECIFICATION

Please replace the following paragraphs as presented in the substitute specification on October 12, 2004, with the paragraphs set forth below.

Page 8, Paragraph 3 beginning at line 10

Platelet-derived growth factor (PDGF) was originally isolated from platelet lysates and identified as the major growth-promoting activity present in serum but not in plasma. Two homologous PDGF isoforms have been identified, PDGF A and B, which are encoded by separate genes (on chromosomes 7 and 22). The most abundant species from platelets is the AB heterodimer, although all three possible dimers (AA, AB and BB) occur naturally. Following translation, PDGF dimers are processed into ~30 kDa secreted proteins. Two cell surface proteins that bind PDGF with high affinity have been identified, α and β (Heldin *et al.* (1981) Proc. Natl. Acad. Sci., 78: 3664; Williams *et al.* (1981) Proc. Natl. Acad. Sci., 79: 5867). Both species contain five immunoglobulin-like extracellular domains, a single transmembrane domain and an intracellular tyrosine kinase domain separated by a kinase insert domain. The functional high affinity receptor is a dimer and engagement of the extracellular domain of the receptor by PDGF results in cross-phosphorylation (one receptor tyrosine kinase phosphorylates the other in the dimer) of several tyrosine residues. Receptor phosphorylation leads to a cascade of events that results in the transduction of the mitogenic or chemotactic signal to the nucleus. For example, in the intracellular domain of the PDGF β receptor, nine tyrosine residues have been identified that when phosphorylated interact with different src-homology 2 (SH2) domain-containing proteins including phospholipase C-g, phosphatidylinositol 3'-kinase, GTPase-activating protein and several adapter molecules like Shc, Grb2 and Nck (Heldin (1995) Cell 80: 213). In the last several years, the specificities of the three PDGF isoforms for the three receptor dimers (αα, α[illegible], and [illegible]) has been elucidated. The α-receptor homodimer binds all three PDGF isoforms with high affinity, the β-receptor homodimer binds only PDGF BB with high affinity and PDGF AB with approximately 10-fold lower affinity, and the α[illegible]-receptor heterodimer binds PDGF BB and PDGF AB with high affinity (Westermark & Heldin (1993)Acta Oncologica 32:101). The specificity pattern results from the ability of the A-chain to bind only to the α-receptor and of the B-chain to bind to both a and [illegible]-receptor subunits with high affinity.

Page 9, Paragraph 3 beginning at line 9

The earliest indication that PDGF expression is linked to malignant transformation came with the finding that the amino acid sequence of PDGF-B chain is virtually identical to that of $p28^{sis}$, the transforming protein of the simian sarcoma virus (SSV) (Waterfield *et al.* (1983) Nature 304:35; Johnsson *et al.* (1984) EMBO J. 3:921). The transforming potential of the PDGF-B chain gene and, to a lesser extent, the PDGF-A gene was demonstrated soon thereafter (Clarke *et al.* (1984) Nature 308:464; Gazit *et al.* (1984) Cell 39:89; Beckmann *et al.* Science 241:1346; Bywater *et al.* (1988) Mol. Cell. Biol. 8:2753). Many tumor cell lines have since been shown to produce and secrete PDGF, some of which also express PDGF receptors (Raines *et al.* (1990) Peptide Growth Factors and Their Receptors, Springer-Verlag, Part I, p 173). Paracrine and, in some cell lines, autocrine growth stimulation by PDGF is therefore possible. For example, analysis of biopsies from human gliomas has revealed the existence of two autocrine loops: PDGF-B/β-receptor in tumor-associated endothelial cells and PDGF-A/α-receptor in tumor cells (Hermansson *et al.* (1988) Proc. Natl. Acad. Sci. 85:7748; Hermansson *et al.* (1992) Cancer Res. 52:3213). The progression to high grade glioma was accompanied by the increase in expression of PDGF-B and the β-receptor in tumor-associated endothelial cells and PDGF-A in glioma cells. PDGF overexpression may thus promote tumor growth either by directly stimulating tumor cells or by stimulating tumor-associated stromal cells (e.g., endothelial cells). The proliferation of endothelial cells is a hallmark of angiogenesis. Increased expression of PDGF and/or PDGF receptors has also been observed in other malignancies including fibrosarcoma (Smits *et al.* (1992) Am. J. Pathol. 140:639) and thyroid carcinoma (Heldin *et al.* (1991) Endocrinology 129:2187).

Page 11, Paragraph 2 beginning at line 3

There is now considerable evidence that PDGF B-chain is a major contributor to the formation of neointimal lesions. In a rat model of restenosis, the neointimal thickening was inhibited with anti-PDGF-B antibodies (Ferns (1991) Science 253:1129-1132; Rutherford *et al.* (1997) Atherosclerosis 130:45-51). Conversely, the exogenous administration of PDGF-BB promotes SMC migration and causes an increase in neointimal thickening (Jawien *et al.* (1992) J. Clin. Invest. 89:507-511). The effect of PDGF-B on SMCs is mediated through PDGF β-receptor which is expressed at high levels in these cells after balloon injury (Lindner and Reidy (1995) Circulation Res. 76:951-957). Furthermore, the degree of neointimal thickening

following balloon injury was found to be inversely related to the level of expression of PDGF β-receptor at the site of injury (Sirois *et al.* (1997) Circulation 95:669-676).

Page 12, Paragraph 2 beginning at line 5

A large variety of progressive renal diseases are characterized by glomerular mesangial cell proliferation and matrix accumulation (Slomowitz *et al.* (1988) New Eng. J. Med. 319:1547-1548) which leads to fibrosis. PDGF B-chain appears to have a central role in driving both of these processes given that 1) mesangial cells produce PDGF *in vitro* and various growth factors induce mesangial proliferation via induction of auto- or paracrine PDGF B-chain synthesis; 2) PDGF B-chain and its receptor are overexpressed in many glomerular diseases; 3) infusion of PDGF-BB or glomerular transfection with a PDGF B-chain cDNA can induce selective mesangial cell proliferation and matrix accumulation *in vivo*; and 4) PDGF B-chain or β-receptor knock-out mice fail to develop a mesangium (reviewed in Floege and Johnson (1995) Miner. Electrolyte Metab. 21:271-282). In addition to contributing to kidney fibrosis, PDGF is also believed to play a role in fibrosis development in other organs such as lungs and bone marrow and may have other possible disease associations (Raines *et al.* (1990) Experimental Pharmacology, Peptide Growth Factors and Their Receptors, Sporn & Roberts, eds., pp. 173-262, Springer, Heidelberg).

Page 41, Paragraph 4 beginning at line 24

Additionally, cancer, angiogenesis, restenosis, and fibrosis involve the production of growth factors other than PDGF. Thus, it is contemplated by this invention that a Complex comprising PDGF Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound, a Lipid Construct comprising PDGF Nucleic Acid Ligand or a Complex comprising a PDGF Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound can be used in conjunction with Complexes comprising Nucleic Acid Ligands to other growth factors (such as bFGF, TGFβ, hKGF, etc.) and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound, a Lipid Construct comprising PDGF Nucleic Acid Ligand or a Complex comprising a PDGF Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound.